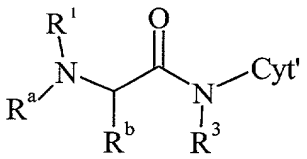
Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof,

wherein

R^1 represents an amino alkanoyl or oligopeptidoyl group, the N-terminal amino function of which is attached to a capping group (Cg) which is capable of enhancing the chemical stability of said compound under physiological conditions and the physical stability of aqueous pharmaceutical formulations comprising said compound;

R^a and R^b together with the interjacent N-C group form an optionally substituted, optionally benzo- or cyclohexano-condensed 3- to 7-membered saturated or unsaturated heterocyclic ring, in which one or two CH_2 groups may also be replaced by NH, O or S;

R^3 represents H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl, aryl or heteroaryl; and

Cyt' represents the residue of a cytotoxic or cytostatic compound.

2. A compound of formula (I) according to claim 1 wherein the capping group exhibits one or more functional groups, which have the capability of forming salts with pharmaceutially acceptable acids or bases, selected from amino, carboxy, phospate, phophonate, sulfate and sulfonate groups.

3. A compound of formula (I) according to claim 1 or 2, wherein said capping group (Cg) is a group of formula

$$R^2\text{-}(CH_2)_m\text{-}Z\text{-},$$

in which

R^2 represents

(f) a group selected from C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl and heteroaryl, wherein each of these groups is substituted by at least one amino, carboxy, phospate, phophonate, sulfate, sulfonate or hydroxy group, or

(g) an optionally substituted 5- to 7-membered saturated or unsaturated nitrogen, oxygen and/or sulfur containing heterocyclic group,

(h) a phenyl group which is substituted by 1 to 5 fluorine atoms;

(i) a C_1-C_6 fluoroalkyl group; or

(j) in the case that m is1, an optionally substituted 5- to 6-membered heteroaryl group;

Z represents –CO-, -O-CO-, -SO_2-, NH-CO- or a single bond;

m is 0, 1 or 2.

4. A compound of formula (I) according to claim 1 or 2, wherein

R^1 represents a residue of formula Cg-A, Cg-B-A or Cg-$(D)_n$-B-A, in which

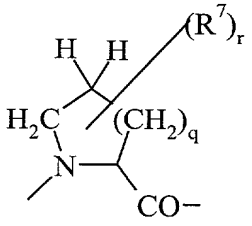
Cg represents a capping group of formula R^2-$(CH_2)_m$-Z-, wherein R^2 is an optionally substituted saturated heterocyclyl or heteroaryl group;

m is 0 or 1;

A, B and D each independently represent moieties derived from amino carboxylic acids of the formula -[NR^4-$(X)_p$-CO]- wherein X represents CR^5R^6 and wherein R^4, R^5 and R^6 each independently represent a hydrogen atom, an optionally substituted C_1-C_6-alkyl, C_3-C_8-cycloalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl group, and

p is 1, 2, 3, 4, 5; or

A, B and D each independently represent moieties derived from cyclic amino carboxylic acids of formula



wherein

R^7 represents C_1-C_6-alkyl, OH, or NH_2,

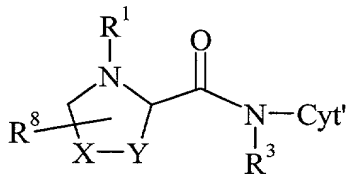
n is an integer from 1 to 10;

q is 0, 1 or 2; and

r is 0, 1 or 2.

5. A compound of formula I according to any of claims 1 to 3, wherein the heterocyclic ring formed by R^a, R^b and the interjacent N-C is substituted by R^8 and R^9, wherein R^8 and R^9 each independently represent a hydrogen or halogen atom or a C_1-C_6-alkyl, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkoxy, thiol, C_1-C_6-alkylthio, oxo, imino, fomyl, C_1-C_6-alkoxy carbonyl, amino carbonyl, C_3-C_8-cycloalkyl, aryl, or heteroaryl group.

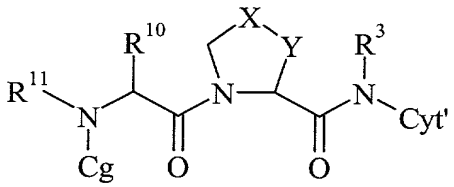
6. A compound of fomula IA



(IA)

wherein R^1, R^3, R^8, Cyt' are as defined in any of the preceding claims, and
X-Y represents CHR^9-CH_2, CR^2=CH, NH-CH_2, CH_2-NH, -CR^9-, CH_2-CHR^9-CH_2.

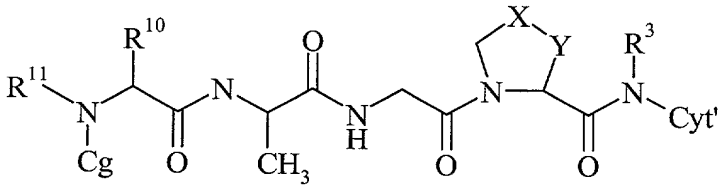
7. A compound of fomula IA1



(IA1)

wherein R^3, Cyt' Cg, X and Y are as defined in any of the preceding claims, and R^{10} and R^{11} each independently represent a hydrogen atom, an optionally substituted C_1-C_6-alkyl, C_3-C_8-cycloalkyl, aryl or heteroaryl group, or
R^{10} and R^{11} together with the interjacent N-C group form an optionally substituted, optionally benzo- or cyclohexano-condensed 3- to 7-membered saturated or unsaturated heterocyclic ring, in which one or two CH_2 groups may also be replaced by NH, O or S.

8. A compound of fomula IA2



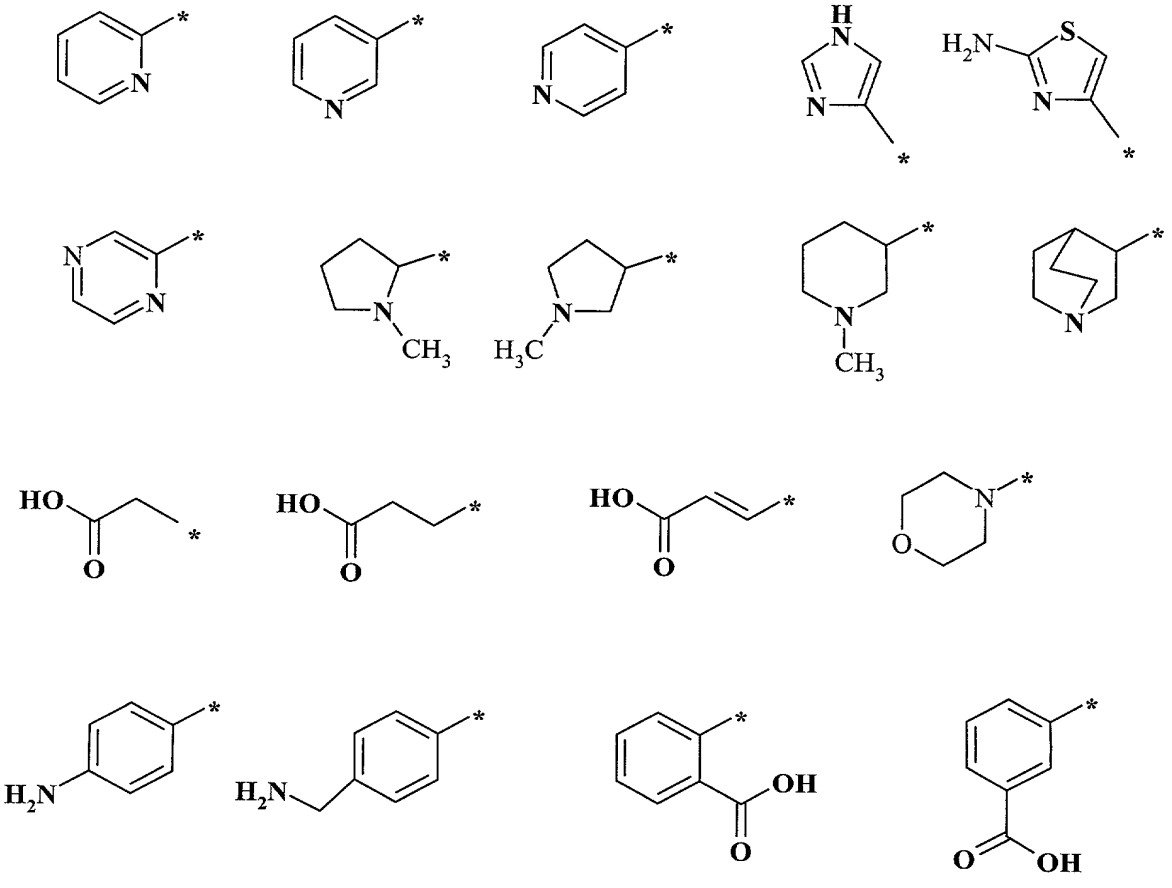
(IA2)

wherein R^3, Cyt' Cg, X and Y are as defined in any of the preceding claims, and R^{10} and R^{11} each independently represent a hydrogen atom, an optionally substituted C_1-C_6-alkyl, C_3-C_8-cycloalkyl, aryl or heteroaryl group or

R^{10} and R^{11} together with the interjacent N-C group form an optionally substituted, optionally benzo- or cyclohexano-condensed 3- to 7-membered saturated or unsaturated heterocyclic ring.

9. Compounds of formulae I, IA, IA1 or IA2 according to any of the preceding claims, wherein

R^2 represents a group selected from



10. A compound according to any of the preceding claim, wherein R^1 represents an aminoalkanoyl, or an oligopeptidoyl group, which is derived from glycine (Gly), or the D- or L-forms of alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp), cysteine (Cys), methionine (Met), serine (Ser), threonine (Thr), lysine (Lys), arginine (Arg), histidine (His), aspartatic acid (Asp), glutamic acid (Glu), asparagine (Asn), glutamine (Gln), proline (Pro), 4-hydroxy-proline (Hyp), 5-hydroxy-lysine, norleucine (Nle), 5-hydroxynorleucine (Hyn), 6-hydroxynorleucine, ornithine, or cyclohexylglycine (Chg) and wherein the N-terminal amino function of said aminoalkanoyl or oligopeptidoyl group is attached to a capping group Cg.

11. A compound of formula I according to any of the preceding claims, wherein the unit A is derived from L-proline, glycine, L-norleucine, L-cyclohexylglycine, L-5-hydroxynorleucine, L-6-hydroxynorleucine, L-5-hydroxylysine, L-arginine, or L-lysine.

12. A compound according to any of the preceding claims wherein R^1 is a group selected from the formulae (1) to (14):

Cg-Gly	(1)
Cg-Nle	(2)
Cg-Val	(3)
Cg-Met	(4)
Cg-Xxx-Gly	(5)
Cg-Xxx-Hyn	(6)
Cg-Xxx-Pro	(7)
Cg-Xxx-His	(8)
Cg-Xxx-Met	(9)
Cg-Xxx-Ala	(10)
Cg-Xxx-Hyn	(11)
Cg-Xxx-Ala-Gly	(12)

$Cg\text{-}(Xxx)_n\text{-}Xxx\text{-}Gly$ (13)

$Cg\text{-}(Xxx)_n\text{-}Xxx\text{-}Ala\text{-}Gly$ (14)

wherein

Cg represents a capping group selected from pyridinyloxycarbonyl, pyridinylacetyl, pyridinylmethylsulfonyl and pyridylmethylaminocarbonyl;

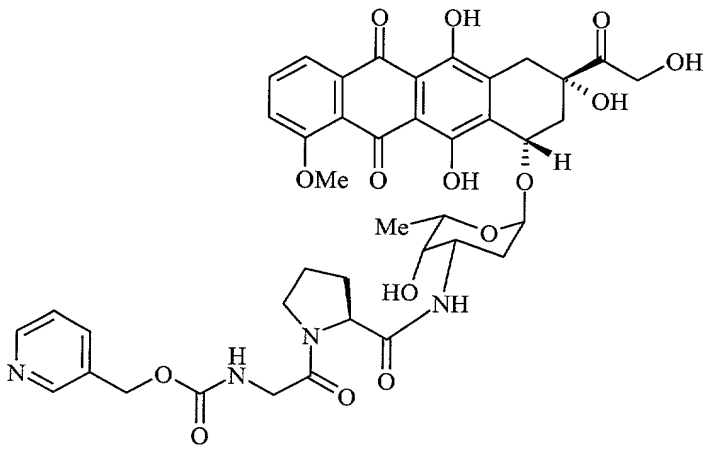
Xxx represents a moiety derived from an amino carboxylic acid; and

n is an integer from 1 to 6.

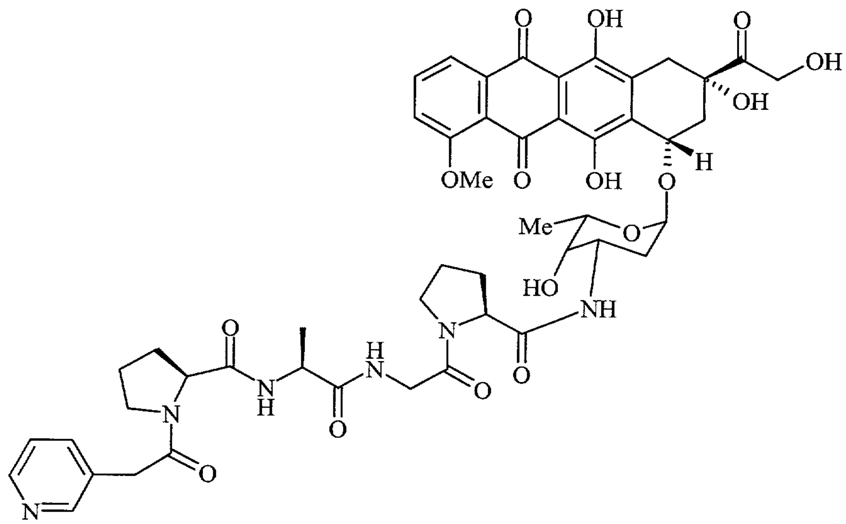
13. A compound according to claim 11 wherein the amino alkanoic acid moieties exist in the (L)-configuration

14. A compound of any one of claims 1 to 12, wherein Cyt' is an anthracycline group.

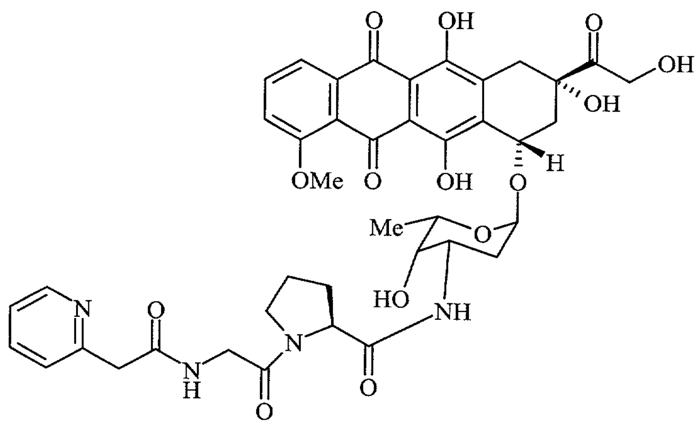
15. A compound of claim 14 selected from the formulae (IIIA) to (IIIH):



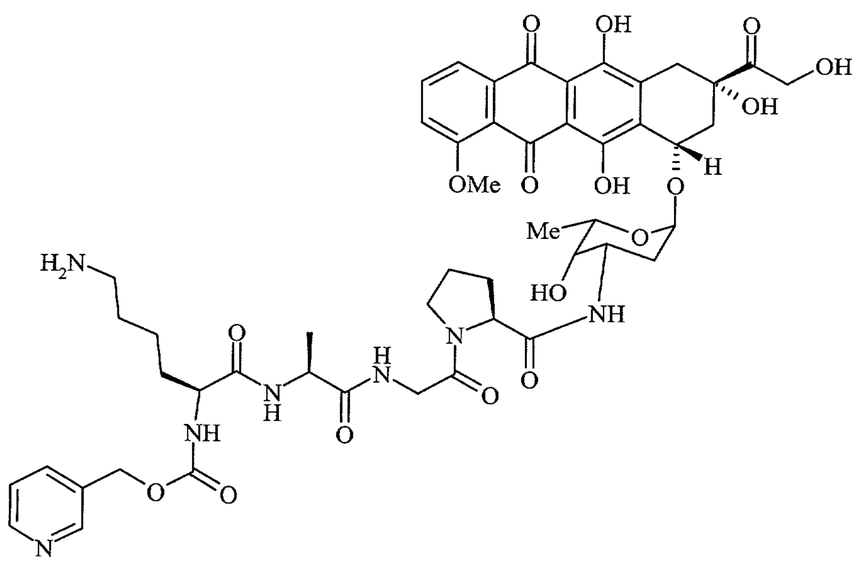
(IIIA)



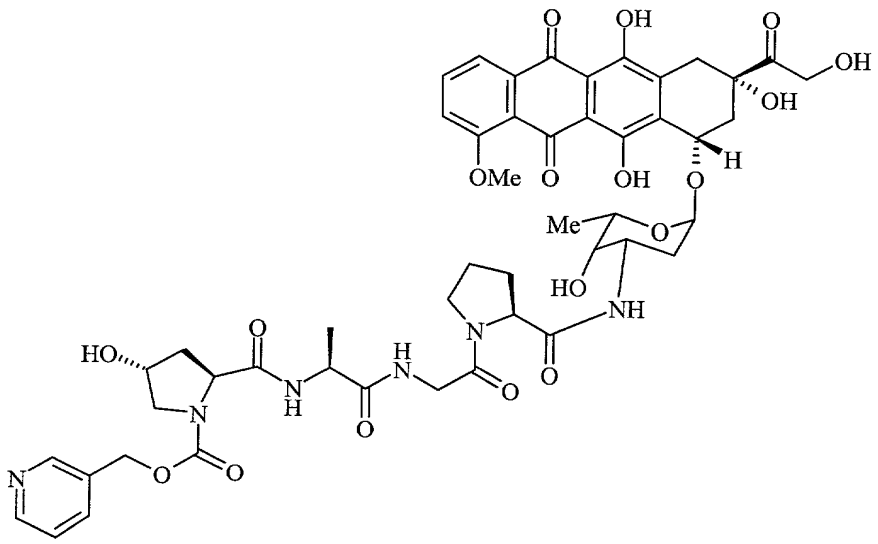
(IIIB)



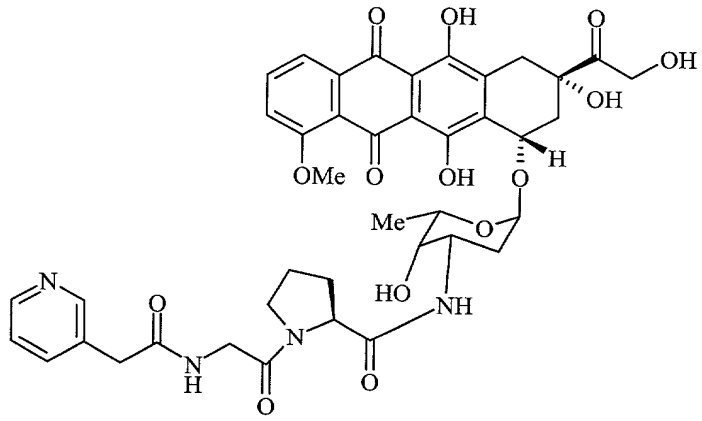
(IIIC)



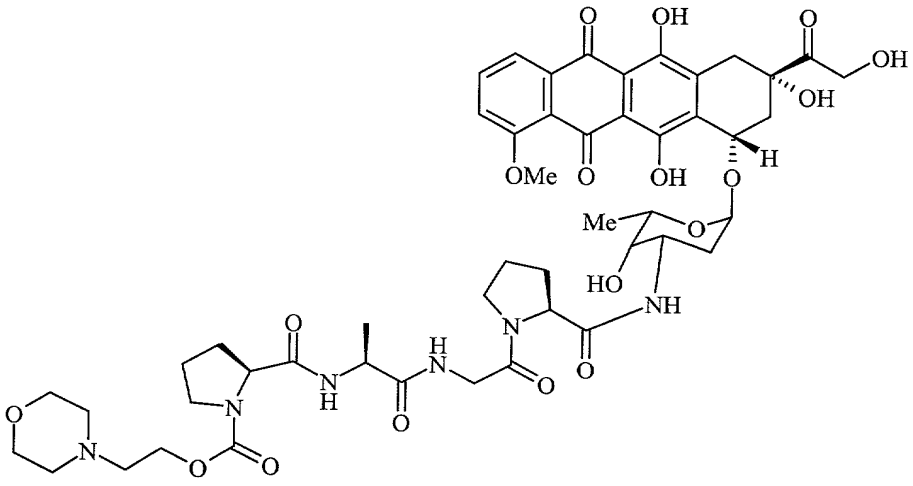
(IIIE)



(IIIF)



(IIIG)



(IIIH)

16. A prodrug that is capable of being converted into a cytotoxic or cytostatic drug, by the catalytic action of FAPα, said prodrug exhibits an oligomeric part comprising up

to 13 amino carboxylic residues, the C-terminal amino carboxylic thereof is recognised by FAPα, and a cytotoxic or cytostatic part, characterized in that the N-terminal amino function of the oligomeric part is attached to a capping group (Cg) which is capable of enhancing the chemical stability of said prodrug under physiological conditions and the physical stability of an aqueous pharmaceutical formulations comprising said prodrug.

17. The prodrug of claim 16 wherein the capping group is a group of formula R^2-$(CH_2)_m$-Z-, in which R^2 represents

(a) a group selected from C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl and heteroaryl, wherein each of these groups is substituted by at least one amino, carboxy or hydroxy group, or

(b) an optionally substituted 5- to 7-membered saturated, unsaturated or aromatic nitrogen containing heterocyclic group, or

(c) a phenyl group which is substituted by 1 to 5 fluorine atoms;

Z represents –CO-, -O-CO-, -SO2-, -NH-CO- or a single bond;

m is 0 or 1.

18. The prodrug of claim 16 or 17, wherein the C-terminal amino carboxilic residue is selected from D-proline, L-proline, D-hydroxyproline and L-hydroxyproline and the oligomeric part comprises two, three, or four amino carboxylic acid residues.

19. A compound of any one of the preceding claims for medical use.

20. Pharmaceutical composition comprising a compound according to any one of claims 1 to 19, and optionally one or more pharmaceutically acceptable excipients.

21. Use of a compound according to any one of claims 1 to 19 in the preparation of a pharmaceutical composition for the treatment of cancer.

22. Method of treatment of cancer, comprising administering a pharmaceutical composition according to claim 20 to a patient.

23. Method of treatment of cancer, wherein a prodrug is administered to a patient wherein said prodrug is capable of being converted into a cytotoxic or cytostatic drug by the enzymatic activity of FAPα, and said prodrug exhibits an oligomeric part comprising up to 13 amino carboxylic residues, the C-terminal amino carboxylic thereof is recognised by FAPα, and a cytotoxic or cytostatic part, characterized in that the N-terminal amino function of the oligomeric part is attached to a capping group (Cg) which is capable of enhancing the chemical stability of said prodrug under physiological conditions and the physical stability of aqueous pharmaceutical formulations comprising said prodrug.

24. Use of a prodrug which is capable of being converted into a cytotoxic or cytostatic drug by the enzymatic activity of FAPα, said prodrug exhibits an oligomeric part comprising up to 13 amino carboxylic residues, the C-terminal amino carboxylic thereof is recognised by FAPα, and a cytotoxic or cytostatic part, wherein the N-terminal amino function of the oligomeric part is attached to a capping group (Cg) which is capable of enhancing the chemical stability of said prodrug under physiological conditions and the physical stability of aqueous pharmaceutical formulations comprising said prodrug, for the manufacture of a stable medicament for the treatment of cancer.